

'INSTEP2'

**INCREASING NOTIFICATIONS OF TUBERCULOSIS FROM
PRIVATE PRACTITIONERS: A RANDOMISED CONTROLLED
TRIAL**

Protocol Number: 1

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale

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STATEMENT OF COMPLIANCE

The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Institutional Review Board (IRB). The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form will be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved.

The sponsor will have no role or authority in: study design; in collection, management, analysis and interpretation of the data; in writing of reports; in the decision to submit reports for publication.

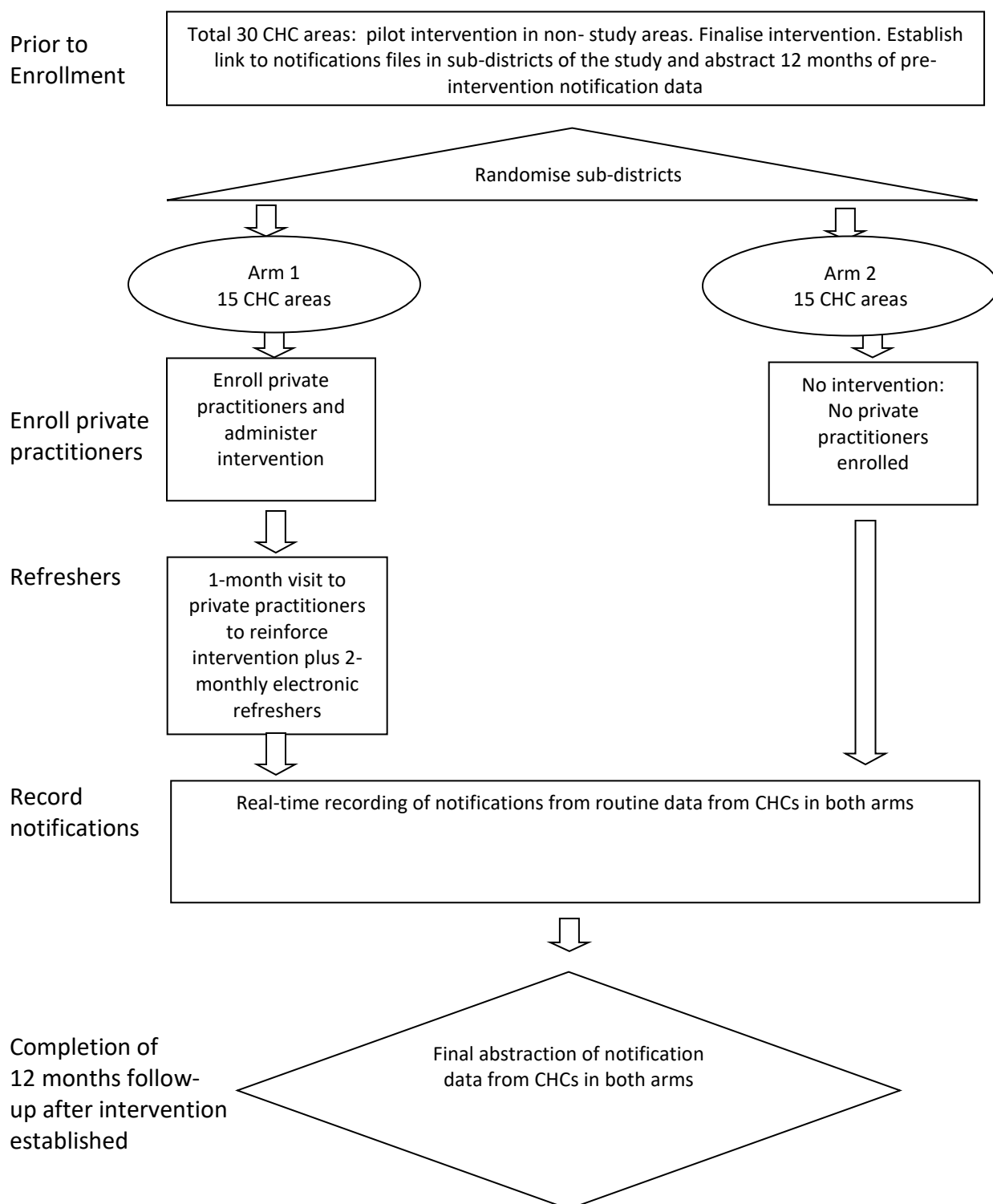
This study is conducted as a collaboration between researchers at Universitas Padjadjaran and the University of Otago, which operates under a signed Memorandum of Understanding.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Increasing notifications of TB cases from private practitioners (PP): a randomised controlled trial
Study Description:	<p>This is a cluster randomised controlled intervention trial. The multi-component public health intervention will be administered to private practitioners in Community Health Centre (CHC) clusters. The change in the number of tuberculosis (TB) notifications over 12 months before, and 12 months after, the intervention will be compared between study arms.</p> <p>Hypothesis related to the Primary Efficacy Endpoint: A tailored intervention in PPs will increase TB notifications.</p>
Objectives:	<p>Primary objective: To evaluate whether a tailored intervention package increases notifications of TB from PPs in Bandung, Indonesia.</p> <p>Secondary objectives: (1) To calculate the proportion of referrals from PPs in the intervention arm that are actually diagnosed with TB; (2) To conduct a restricted analysis of the primary endpoint, limited to notifications of patients who live in the CHC area where they are notified.</p>
Primary Endpoint:	The primary endpoint is the change in the number of notifications of TB from the 12 months before to the 12 months after the intervention is fully implemented. This change in the number of notifications will be compared between intervention clusters (n=15) and control clusters (n=15).
Study Population:	All those living in the 30 CHC clusters
Phase:	Pragmatic public health intervention efficacy trial.
Description of Sites/Facilities Enrolling PPs:	The intervention will be administered to PPs in areas around 15 CHCs (clusters), at their place of practice. PPs in the control areas will receive no intervention.
Description of Study Intervention:	(1) An electronic referral and notification system; (2) Education about signs and symptoms of TB and TB management; (3) An individualised practitioner plan for diagnostic and management pathways.
Study Duration:	3 years
PP involvement Duration:	2 years
Sub-study	<p>Sub-study objectives: On notified TB cases, to use social network analyses, whole genome sequencing and phenotypic drug susceptibility testing to inform clinical algorithms for drug resistant-TB and the design of a transmission study.</p> <p>Study population: Pulmonary TB cases in selected study intervention clusters (sub-study)</p> <p>Description of study: <i>M. tuberculosis</i> isolates from 150 notified TB cases will be sequenced and genomic and phenotypic drug susceptibility test results compared. Social network data from interviews and genomic data will be combined to explore transmission of <i>M. tuberculosis</i> to inform design of a future study.</p>

1.2 SCHEMA



1.3 SCHEDULE OF ACTIVITIES (SOA)

	Pre-enrollment	Enrollment/Baseline Visit 1, Day 1	Study Visit 2 Month 1	Electronic refresher Month 2	Electronic refresher Month 4	End of follow-up (12 months after intervention rolled out)	Post-completion of data collection
Procedures							
Informed consent		X					
Demographic data collection		X					
Administer study intervention		X					
Complete initial visit form		X					
Complete follow-up visit form			X				
Extract notification data	X					X	
Analysis and report writing							x

Overall timeline summary:

Year 1:

Months 1-6: Finalise protocol, complete design and piloting of intervention, including app. Pre-intervention data abstraction.

Months 7-12: Implement intervention

Year 2:

Months 1-5: Complete intervention

Months 6-12: Commence follow-up period

Year 3

Months 1-6: Complete follow-up and data abstraction

Months 7-12: Analysis and write-up

2 INTRODUCTION

2.1 STUDY RATIONALE

Tuberculosis (TB) is the third leading cause of death in Indonesia. The 2014/15 TB prevalence survey estimated that there were 1 million cases of TB, second only to India globally for burden of TB.(1) Disturbingly, the prevalence survey showed that over half of TB cases in Indonesia are not notified. The huge private sector in Indonesia, comprising an estimated 70,000 practitioners, provides over 50% of health care but notifies less than 10% of all diagnosed TB cases.(2) TB patients managed in the private sector are often treated sub optimally and have poorer outcomes.(3, 4) The majority of people with symptoms of TB initially engage private practitioners (PPs), but 80% of the facilities they attend cannot diagnose TB.(5) As part of advancing Public-Private Mix (PPM) the government made TB notification

mandatory in 2016, but intervention is likely to be needed for notifications to increase substantially. Such intervention needs to be based on a sound understanding of contextual factors around PPs and how they relate to the public sector with respect to the diagnosis, treatment and reporting of TB cases.

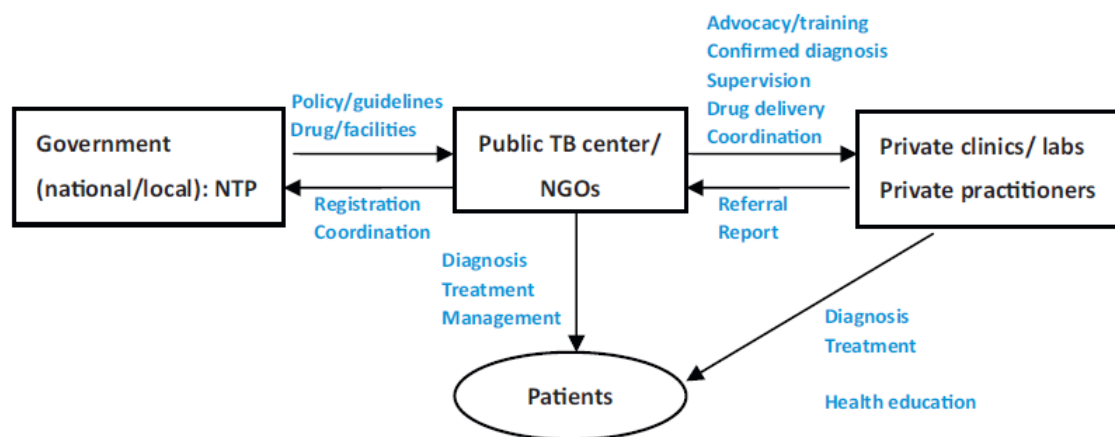
2.2 BACKGROUND

PPM can impact all aspects of TB suspect management pathways (see figure below). Indonesia is committed to enhancing PPM to improve TB control.(6) An initial focus was on private-public hospital partnerships.(7) The benefits of PPM initiatives have yet to be fully realized across the country.(8)

We have been conducting research to inform the design of interventions to increase notifications of TB from PPs in Indonesia. PPs are medically trained general practitioners or specialists. They work outside government Community Health Centres (CHC), either in solo practice or private clinics. When they diagnose TB patients, they are supposed to refer and notify them to the CHC or other DOTs treatment facility. Some have an agreement with the CHC to continue to treat their patients using free TB drugs supplied by the government. In a feasibility study of a mobile ‘app’ for notification,(9) we showed that 40% of participating PPs have inadequate knowledge of TB symptoms and/or signs. The app was well received, utilized, and showed potential to increase TB notifications, although not all PPs had phones that supported it. We are currently conducting a USAID funded project, ‘INSTEP’, to describe and understand the health care pathways of patients seeking treatment for TB, and of PP practice. We have discovered that only 65% of officially registered PPs can be found. We have identified 245 of 1200 PPs in the 30 study areas that had diagnosed at least 1 TB case in the previous 3 months (total n=870 TB cases) - less than 20% had been notified. In 2018, we are exploring patient diagnostic pathways and PP diagnostic and treatment practices.

With our recent studies, a strong relationship with the National TB Control Programme, and our proven track record in intervention trials, our collaborative team is in a strong position to refine and evaluate an intervention in PPs. The primary goal of this randomised controlled trial is to increase notifications of TB by PPs through a tailored intervention.

Figure. Schematic diagram of a generic PPM. Reproduced from Lei et al.(10)



2.3 RISK/BENEFIT ASSESSMENT

The risk of any referral for TB treatment is over treatment i.e. treatment of individuals for TB who do not actually have TB. These individuals are placed at risk from side effects of TB medications. However, part of the intervention is to work with the practitioners to identify an appropriate diagnostic approach to their patients and the risk is further outweighed by the risk of TB cases being managed with the wrong medications in the wrong way, if not referred for treatment to the National TB Programme (NTP). Furthermore, we plan for the paperwork for notifications to be done by the NTP, after confirmation of the patients' diagnoses following referral. There are no obvious risks to PP's health or safety of receiving this public health intervention.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS/KEY MEASURES
Primary	
To evaluate whether a tailored intervention package increases notifications of tuberculosis (TB) by private practitioners in Bandung, Indonesia.	The primary endpoint is the change in the number of notifications of TB from the 12 months before to the 12 months after the intervention is fully implemented.
Secondary objectives of trial	
To compare the proportion of referrals from PPs in the intervention and control arms that are actually diagnosed with TB	The change in proportion of referrals from PPs in the intervention arm that are actually diagnosed with TB from the 12 months before to the 12 months after the intervention is fully implemented.
To conduct a restricted analysis of the primary endpoint, limited to notifications of patients who live in the CHC area where they are notified.	The same as primary endpoint, restricted to notifications of patients who live in the CHC area where they are notified.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Hypothesis related to the Primary Efficacy Endpoint: A tailored intervention in PPs will increase TB notifications.

This is a cluster randomised controlled trial of a multi-component public health intervention to increase notifications of TB from PPs in one city, Bandung, in Indonesia. Clusters are CHC areas and the intervention

will be administered directly to PPs in sub-districts randomised to the intervention arm. The CHCs in both arms will be informed about the study and asked, through the National TB Control Programme, to make their notification data available and their willingness will be recorded. No intervention will be given to PPs in the control arm. Notifications will be obtained directly from routine records, with accompanying information gathered about the address of the patient and referring doctor. Notified TB cases are, by definition, TB cases who have been commenced on TB treatment, noting that some referred 'TB cases' will be diagnosed as not having TB by CHC staff. Data on address of the patient will identify the extent of the 'contamination' between arms.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Cluster randomisation of sub-districts is required because individual PPs within the cluster are likely to relate to the same CHC and thereby potentially be influenced by that CHC. Individual randomisation, therefore, would be subject to greater contamination. There will still be some contamination between arms due to peculiarities of PP practice and individual patient health seeking behaviour (as described in the statistical considerations section). The control arm will simply continue standard practice; a placebo is not indicated.

4.3 END OF STUDY DEFINITION

The end of the follow-up is defined as the last day of the 12-month period of observation post-intervention. The end of the study is the end of the following 6 month period of analysis and write up.

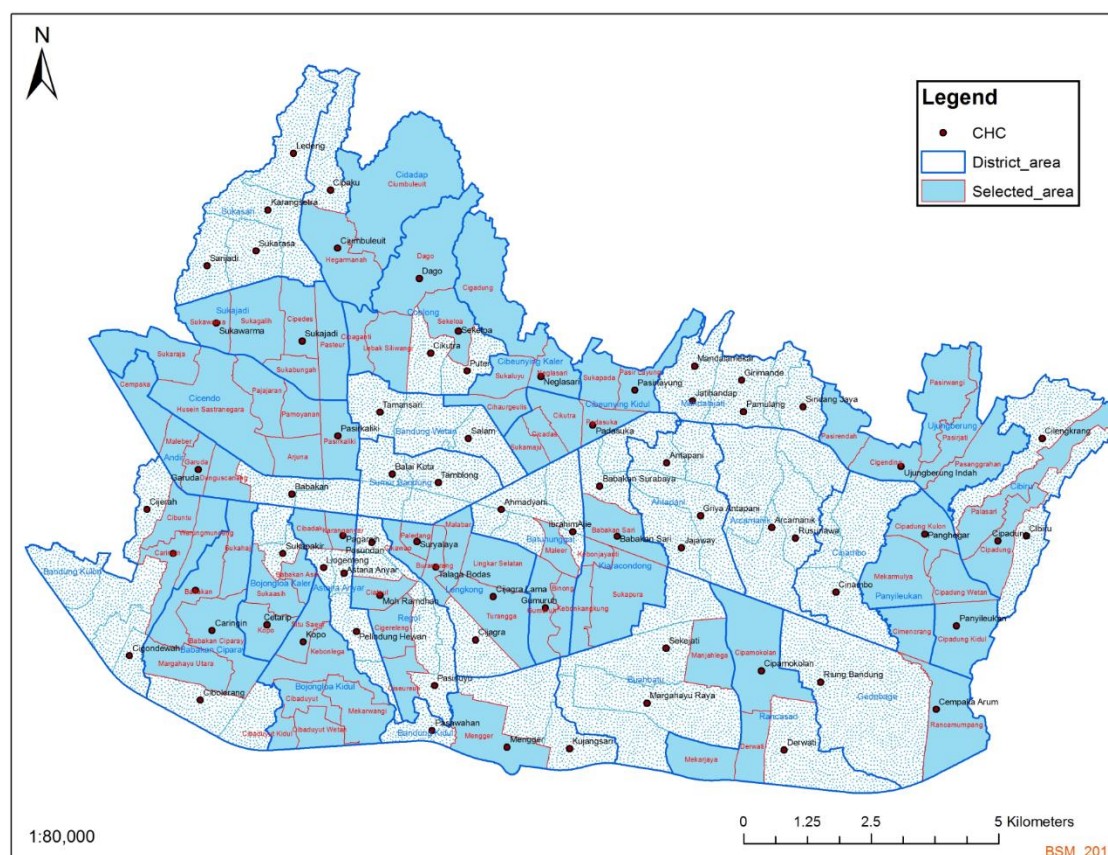
5 STUDY POPULATION

5.1 INCLUSION AND EXCLUSION CRITERIA

Of 73 Community Health Centre (CHC) areas in Bandung, 30 were randomly selected for the INSTEP study, proportional to their catchment population's size, and will be included in the RCT. Bandung is divided into sub-districts (see map below). Some sub-districts have more than one CHC, while CHC each still have defined catchment populations. The map therefore shows 22 sub-districts where the 30 CHC areas are found.

The study population consists of all the people who may visit a PP in any of the study areas during the year before and the year after the intervention – outcome is measured on all people who visit a PP in a study area, are diagnosed with suspected TB and reported to the CHC.

Figure. Selected (blue shaded) areas for the INSTEP study and intervention trial.



5.2 STRATEGIES FOR RECRUITMENT AND RETENTION

Outcome data are all obtained from routinely collected data, so processes for retention of individuals are not required. Recruitment is at the cluster level, and only PPs in intervention clusters are contacted to receive the intervention. The details for that process are given in section 6.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 RECRUITMENT AND ELIGIBILITY OF PPS

All medically qualified PPs in the CHC in the intervention arm who reported having diagnosed at least one TB case in the past 3 months when visited in the INSTEP study will be eligible for the intervention. They will intend to work in the current location for the duration of the study as their primary place of private practice.

They will be excluded from the intervention if:

- they are unable to use an electronic device for referral;

- more than 3 months of non-practice during the study period is anticipated;
- they are not a qualified medical practitioner, with the appropriate medical authority in Indonesia

Through the INSTEP study, we identified that 245 of 1200 PPs in the 30 CHC areas had diagnosed at least 1 TB case in the previous 3 months (total n=870 TB cases from 245 PPs) and less than 20% had been notified. The study will be conducted starting mid-2019, flowing directly on from the INSTEP study to minimize the effect of PPs exiting the areas. We will personally approach, at their place of work, each of the 245 PPs identified above who are in the intervention arm (approximately half). They will be fully informed about the study, invited to participate and provide written informed consent. A schedule will be generated for their education and their follow-up (every 2nd month). We expect around 80% of approached PPs will be willing to participate in the study.

PPs participating in the intervention will have the non-financial incentive of a certificate of proficiency issued by the Indonesian Medical Association that provides them with credits that can be used as proof of continuing medical education for renewing their license to practice.

6.1.2 INTERVENTION

The Intervention will comprise:

1. An electronic referral and notification system, based on evolution of the mobile 'app' designed for the feasibility study;
2. A standardized education about the signs and symptoms of TB and TB management;
3. An individualised plan for each PP with respect to their approach to the diagnosis and management of TB suspects, considering the type of PP and their context.
4. 1 month follow-up visit from the study team.
5. 2-monthly electronic reminder/refresher.

6.2 PREPARATION/FINALISATION OF INTERVENTION PACKAGE

1. Electronic system. This system is a refinement of the electronic referral and report-back system using a mobile phone 'app' that was developed in collaboration with information technology (IT) at Telkom University, Bandung.(9) The system will enable essential data to be uploaded, consistent with National TB Control Programme forms, including: patient identity, symptoms, diagnostic examinations, TB type, treatment, and follow-up care. Inputted information will be sent to a secure centralised server and will be able to be monitored through log-in by the authorized individuals in a web-based application that is compatible with both android and apple operating systems. Any PPs without a compatible cell phone will be provided with one, and internet connection issues will be addressed. The system includes a reminder system so the PPs can complete patient management steps and it will provide an electronic education refresher every second month. Piloting will include final consultation with the National TB Control Programme, who have an interest in electronic notification.

2. Education. This is a refinement of the education package that we developed for the feasibility study. It is focused on TB suspect identification, provisional diagnosis and referral, including how to use the mobile phone 'app'. Since we found in the feasibility study that not all PPs have time to attend a 1-day training, the education will be two 2-hour sessions (one to each individual at their place of work and the other in groups) and electronic follow-up (see above). A certificate of proficiency will be available from the Indonesian Medical Association, which can be used towards meeting continuing medical education requirements.
3. Patient management pathways. Data from the INSTEP study will inform individualised agreed patient management pathways for each PP. The INSTEP study is conducting patient pathway analyses through a survey of TB cases (n=400), quality assessment through standardized patients attending PPs (n=20) and key informant interviews and focus groups of PPs, stakeholders and patients (n=50). These data will inform, for each PP, a simple individualised approach for the management of TB suspects, which takes into account the context around each PP's practice, identifying the most efficient and feasible approach to obtaining a diagnosis and notifying TB patients.(11)
4. Piloting. The intervention package will be piloted with 10 PPs who practice outside of the 30 selected CHC areas, over one month. Following feedback from the PPs and study staff, it will be refined further and finalised for the start of the implementation period in the second half of year 1.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomisation: Using the randomly selected areas from the previous INSTEP study, we will randomly select 15 areas as intervention areas, repeating the randomisation 100 times. From this we will select the 10 allocations that meet the criteria of i) including having the least number of adjacent CHC areas between intervention and control arms, to minimize contamination between the arms, and ii) balancing by CHC numbers of TB cases diagnosed per annum. Then we will randomly select the final allocation from those 10.

Trial randomisation codes will not be broken until the study is closed and analysis is commenced. Since there are no anticipated serious adverse events, no criteria for breaking the codes have been set.

Investigators and CHC staff will not be blinded to study arm as this is not practical in this type of trial. Because of the electronic referral from PPs in the intervention arm, the clinics receiving and recording notifications will be aware of which study arm they are in. Staff conducting diagnostic investigations (laboratory personnel and radiologists) will not be part of the study team and will be blinded to study arm. Notification data will be abstracted from routine records so they will not be influenced by study staff.

Diagnosis of TB cases: It is expected that the notifications from referrals by PPs will be a mixture of TB cases diagnosed by sputum test, x-ray, and clinical presentation only. This will be captured through the app. We will record the basis of diagnosis for each notified case, classifying each as 'definite', 'probable',

‘possible’ or ‘not TB’, using a standard operating procedure (SOP). This will enable a secondary analysis, showing the proportion of referrals by PPs that probably don’t have TB and whether the mix of notified TB cases changes with respect to the basis of their diagnosis.

6.4 STUDY INTERVENTION COMPLIANCE

Once the PPs have received the intervention, real-time monitoring of referral practice of patients for diagnosis and notification will be undertaken through the web-link to the app. At the 1-month visit, adherence to the intervention will be assessed according to pre-determined indicators, and a standard form filled with the results. At the end of the visit, any issues will be rectified through re-education. The intervention period will then be complete, while electronic refreshers will continue.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participating PPs are free to withdraw from the intervention at any time upon request.

An investigator may discontinue or withdraw a PP from the intervention for the following reasons:

- PP unable to receive the study intervention within 1 month.
- If the PP meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for PP discontinuation or withdrawal from the study will be recorded on a specific form.

7.2 LOST TO FOLLOW-UP

No PPs will be lost to follow-up, but will be considered lost to intervention if he or she is not able to be found on the scheduled visit, no activity related to the app is occurring, and is unable to be contacted by the study site staff. The following actions will be taken under such a circumstance:

- The study staff will attempt to contact the PP, schedule a visit and counsel the PP on the importance of activity in the study and ascertain if the PP wishes to and/or should continue in the study.
- Before a PP is deemed lost to intervention, the investigator or designee will make every effort to regain contact with the PP (where possible, 3 telephone calls and, if necessary, a certified letter to the PP’s last known mailing address or local equivalent methods). These contact attempts will be documented in the PP’s record or study file.
- Should the PP continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of “lost to intervention”.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

To support the determination of efficacy, as per the primary objectives, data abstraction from routine notification data will be done by trained researchers. The 12-month period before intervention commences will be defined clearly and data abstraction will take place as soon as possible at the end of this period. The 12-month follow up period will be defined clearly. The start date will be immediately after the last PP to receive the intervention has had their 1-month follow up visit. Data abstraction will be done as soon as possible after this 12-month period is completed.

8.2 SAFETY AND OTHER ASSESSMENTS

8.2.1 SAFETY

The following procedures and evaluations will be done as part of the study to monitor safety.

- Interviews: all interviews of PPs will be conducted in private and in confidence, under a standard operating procedure (SOP).

8.2.2 PRIVATE PRACTITIONERS

The following information will be collected, onto a form, from PPs in the intervention arm who undergo intervention: name, gender, age, and self-reported number of TB cases diagnosed in the last 3 months. This will enable comparison of basic characteristics between those who participate in the intervention and those who don't.

8.2.3 TB PATIENTS

The following data will be abstracted from routine records of TB cases at the CHCs: Referring facility/practitioner, date, gender, patient identification, patient address (to the level of CHC area), sputum status, basis of TB diagnosis.

PPs who refer patients for confirmation of diagnosis and notification will enter the following data about the patient into the app: name, gender, age, basis of presumptive/definitive diagnosis, other practice addresses.

Inputted information from PPs will be sent to a secure centralised server and will be able to be monitored through log-in by the authorized individuals in a web-based application that is compatible with both android and apple operating systems.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

It is not expected that this public health intervention will be associated directly with any adverse events or serious adverse events in TB patients.

Staff involved in administering the intervention to PPs are at risk of accidents related to travel to and from the place of work of PPs.

Patients diagnosed with TB by PPs are at risk of over-treatment from mis-diagnosis. However, this should be reduced, rather than increased as in this study they are referred for confirmation of diagnosis and subsequent notification by the National TB program.

8.3.1 EVENTS OF SPECIAL INTEREST

Events that merit reporting to the study leadership include failures such as malfunction of the app and loss of network connection for periods of time. These will be reported using a specific form.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI’s name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;

- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs will be reported to the IRB and to the DCC/study sponsor within 1 month of the investigator becoming aware of the problem.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary outcome: A tailored intervention package for private practitioners increases notifications of tuberculosis (TB) in Bandung, Indonesia.

9.2 SAMPLE SIZE DETERMINATION – KEY CONSIDERATIONS

Less than 10% of PPs work privately in more than one CHC area. Those who also practice within the public system should not affect notifications from that public system, as it has a high notification rate (>95%) already.

While the majority of notified TB patients are diagnosed and treated in their own CHC area, a number are diagnosed outside of their 'home' CHC area (up to 35%; INSTEP study). Those from a different CHC area will have an approximately 1 in 5 chance of being from another intervention area, 1 in 5 chance of being from a control area, and 3 in 5 chance of being from a non-study CHC area (n=43 non-study CHC areas within Bandung). Therefore 'contamination' of the intervention into control areas is estimated to be <10% ($35\% \times 1/5 = 7\%$).

We will have data on the number of individuals from CHC areas outside the intervention areas who are notified by PPs in the intervention arm. Any change in notifications in the control arm will also provide insight into contamination. The primary analysis will compare the change in total number of notifications of patients between intervention and control areas.

Assuming (1) PPs in each arm diagnose at least 500 TB patients in 12 months (INSTEP data); (2) 65% of PP TB diagnoses are patients from their CHC area and 35% are from outside their area; and (3) a 15% baseline notification rate changing to 50% post-intervention in the intervention arm: PP notifications in the control arm areas will change from 75 to 87 notified cases while the change will be from 75 to 201 cases in the intervention arm. Total notifications (adding 475/arm from non-PP) will change from 550 to 562 and 550 to 676 respectively.

Taking the above into account, we will have approximately 90% power to detect a rate ratio of 1.2 (676/562) at the $p=0.025$ level (one sided).

9.3 STATISTICAL ANALYSES

9.3.1 GENERAL APPROACH

The primary analysis will be intention-to-treat, where all patients notified by intervention and control PPs to a CHC will be included. Analysis will be carried out at the cluster level, taking into account correlations within a cluster. 95% confidence intervals will be calculated and a significance level of 0.025 (one-sided) will be used.

9.3.2 BASELINE DESCRIPTIVE STATISTICS

Study arms will be compared on baseline characteristics, including demographics of the PPs and the diagnosed TB cases, using descriptive statistics. No inferential statistics will be used.

9.3.3 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

For the primary trial analysis we will estimate the rate ratio comparing TB notifications in the intervention and control groups. A generalised mixed model will be used with repeated measures of TB notification (pre- and post- intervention) and treatment* time interaction, a log link, Poisson errors and a random effect for PKM to account for over-dispersion.

9.3.4 ANALYSIS OF THE SCONDARY EFFICACY ENDPOINT(S)

1. The proportions of true TB cases among the reported TB cases will be compared in intervention and control arms using a generalised estimation equation. The model will be fit to repeated measures of the proportions of true positive TB notifications for each CHC (pre- and post-intervention) with a treatment by time interaction, a log link, and Poisson errors, with robust standard errors to allow for both the binary data and over-dispersion.
2. The primary trial analysis will be repeated excluding patients who were notified by a PP from a different CHC to their area of residence.

9.3.5 PLANNED SAFETY ANALYSES

There are no planned safety analyses

9.3.6 PLANNED INTERIM ANALYSES

There is no plan to conduct an interim analysis.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing the study are given to the head of each CHC institution. For PPs undergoing intervention, consent forms describing in detail the study intervention, study procedures, and risks are given to the PP and written documentation of informed consent is required prior to starting intervention/administering study intervention. The consent forms are provided as an attachment.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Consent forms will be Institutional Review Board (IRB)-approved and the PP will be asked to read and review the document. The investigator will explain the research study to the participant PP and answer any questions that may arise. A verbal explanation will be provided in terms suited to the PP's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research PPs. PPs will have the opportunity to carefully review the written consent form and ask questions prior to signing. The PPs will have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The PP will sign the informed consent document prior to any intervention. PPs will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the PPs for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before any intervention. The rights and welfare of the PPs will be protected by emphasizing to them that there will be no negative repercussions if they decline to participate in this study, including no reporting of discontinuation to government authorities.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to participating CHC, PPs, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform participating CHCs, PPs, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Participating PPs will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension of this study include, but are not limited to:

- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

The study may resume once any concerns are addressed, and satisfy the sponsor, and IRB.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participating PPs confidentiality and privacy is extended to cover any information relating to them. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), may inspect all documents and records required to be maintained by the investigator. PPs' contact information will be securely stored for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

PP research data, which is for purposes of statistical analysis and scientific reporting, will be stored. This will not include the PP's contact or identifying information. Rather, individual PPs and their research data will be identified by a unique study identification number. The study data entry and study management systems will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored. After the study is completed, the de-identified, archived data will be transmitted to and stored, for use by other researchers including those outside of the study. Permission to transmit data will be included in the informed consent.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator
<i>Philip Hill, MBChB MPH, MD, FRACP, FNZCPHM, Professor</i>
<i>University of Otago, New Zealand</i>

Address	University of Otago Medical School, PO Box 56, Dunedin 9054, New Zealand
Phone Number	+64 21 279 7214
Email	philip.hill@otago.ac.nz

Other Investigators	Institution	Role
Dr Sue McAllister	<i>University of Otago</i>	<i>Epidemiologist, trial documentation and site visit monitoring</i>
Assoc Prof Katrina Sharples	<i>University of Otago</i>	<i>Trial Statistician</i>
Prof Reinout van Crevel	<i>Radboud University</i>	<i>Physician</i>
Dr Bachti Alisjahbana	<i>University of Padjadjaran</i>	<i>Site- PI, Indonesia</i>
Dr Lidya Chaidir	<i>University of Padjadjaran</i>	<i>Molecular Biologist, lead for microbiology and key co-investigator for pathogen genomics</i>
Dr Bony Lestari	<i>University of Padjadjaran</i>	<i>Clinical epidemiologist</i>
Dr Panji Hadisoemarto	<i>University of Padjadjaran</i>	<i>Clinical epidemiologist, trial 'manager' responsible for the running of the project overall in Indonesia.</i>
TBA	<i>University of Padjadjaran</i>	<i>Data manager</i>
Prof Megan Murray	<i>Harvard University</i>	<i>Epidemiologist, member of overall project steering group and lead for Social networking and genomic epidemiology study</i>
Chuan-Chin Huang	<i>Harvard University</i>	<i>Bio-informatics specialist</i>

The project will have an **Executive committee** comprising the PI, and one representative from each major partner – Dr Alisjahbana and Prof Megan Murray. The group will meet electronically every three months to discuss strategic aspects of the project and may invite specific co-investigators to join certain meetings.

The trial will have a **Data Monitoring Committee (DMC)** comprising the PI, lead statistician (Co-I Sharples) and The DMC will operate under a charter and will review data on study conduct.

The project will have a **Project Management Group (PMG)** comprising Co-I Hadisoemarto, the data manager, Co-I Chaidir, and.....The PMG will operate under a charter.

10.1.6 SAFETY OVERSIGHT

Safety oversight by a Data and Safety Monitoring Board (DSMB) will not be required for this public health intervention trial. However, an internal Data Monitoring Committee (DMC) will be established to oversee the study, focused on data quality.

10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

A quality management plan will be developed to describe a site's quality management. Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be automatically generated on a weekly basis and any quality issues identified will be reviewed by the DMC and a plan put in place for resolution.

Following written Standard Operating Procedures (SOPs), visiting investigators (Dr Sue McAllister or substitute) will verify that the trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol.

The investigational site will provide direct access to all source data/documents, and reports for the purpose of the verification visits.

10.1.8 DATA HANDLING AND RECORD KEEPING

10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each PP enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents will be consistent with the data recorded on the source documents.

Clinical data, and clinical laboratory data, will be entered into REDCAP(12) electronic database. The data system includes password protection and will be checked automatically for data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.8.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 10 years after completion of the trial. These documents should be retained for a longer period, however, if required by local regulations. No records

will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.9 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the PPs, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, and reported according to the reviewing IRB requirements.

10.1.10 PUBLICATION AND DATA SHARING POLICY

This study is not subject to any particular publication and data sharing policies and regulations.

10.1.11 CONFLICT OF INTEREST POLICY

Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

11 SUB-STUDY

11.1 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
On notified TB cases, to use social network analyses, whole genome sequencing and phenotypic drug susceptibility testing to inform clinical algorithms for drug resistant-TB and the design of a transmission study.	Concordance between phenotypic and genotypic DST results. Single nucleotide polymorphism (SNP) differences between <i>M. tuberculosis</i> strains. Concordance between SNP differences and social/spatial network analyses

11.2 BACKGROUND/RATIONALE

We will use whole genome sequencing (WGS) of *M. tuberculosis* isolates from notified TB cases to identify drug resistant mutations (to inform clinical algorithms with respect to drug resistance), and to combine with social network analyses to provide preliminary data for designing a larger study of *M. tuberculosis* transmission. WGS has great potential as a tool in the fight against TB drug-resistance, especially in combination with routine surveillance.(13) WGS directly from the first positive culture of TB cases could be used to complement and ultimately replace phenotypic drug susceptibility testing (DST). It could detect resistance to most if not all antibiotics within 24 hours, as demonstrated already.(14) We are conducting a series of studies to explore the introduction of WGS in this way into practice in Indonesia. As part of this, contextual studies that document circulating resistance mutations in the local population are of great benefit. WGS could provide the ultimate molecular resolution for epidemiological typing at the population level, which has previously been an unrealistic aspiration in many lower and middle- income countries. WGS technology is likely to bypass more traditional impractical and less precise typing methods.(15, 16) Emerging strains (17) can be identified and changes in strain diversity can be monitored, reflecting relative prominence of recent or past transmission. A high sampling fraction (the proportion of all TB cases in a population that have an isolate typed), more possible when cases from both private and public health facilities are captured, reduces the misclassification of clusters and of recent versus remote transmission.(18) The combination of high precision genotyping, expanded social network questionnaires and network analyses provides opportunity to explore *M. tuberculosis* transmission.(16, 19, 20)

11.3 OVERALL DESIGN

In real-time, we will culture *M. tuberculosis* isolates from 150 consecutively notified TB cases in purposively (contiguous) selected CHCs in the intervention arm, which is expected to have the highest sampling fraction because of a successful public health intervention. They will have whole genome and phenotypic drug susceptibility testing, enabling comparison between the two tests, to inform clinical algorithms for suspected drug resistant TB. Notified cases will be interviewed and undergo a social network questionnaire. Relatedness according to sequencing data will be linked to social network and spatial analyses to explore possible transmission events and inform design of a large *M. tuberculosis* transmission study.

Identification of drug resistance, phenotypically and/or genotypically, will be reported to the patient's attending doctor, regardless of the time since the sputum specimen was taken.

11.4 INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria: Diagnosed as a case of pulmonary TB in one of the purposively selected CHC intervention areas within the designated follow-up period. Lived the majority of the time in the selected CHC area during the study period.

Exclusion criteria: TB cases unable to produce sputum for culture; sputum smear negative; <14 years of age

11.5 CONSENT, ASSESSMENTS AND PROCEDURES

Each notified TB case, at each CHC selected for the sub-study will be asked by the CHC staff if they are willing to be part of a research study and consent for their name and contact details to be passed on to the researchers. If they consent to this, they will be contacted by research staff, fully informed about the study, invited to participate and provide written informed consent. Consent forms for the sub-study TB patients are attached to this protocol. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any data gathering or investigations. Participants will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before any intervention. The rights and welfare of the participants will be protected by emphasizing to them that there will be no negative repercussions if they decline to participate in this study, including no reporting of discontinuation to government authorities.

The following data will be collected, onto a form, from newly diagnosed pulmonary TB cases enrolled in the sub-study: name, gender, age, street address and geo-coordinates, symptoms, diagnostic examination results, TB type, treatment, and follow-up care. A specific social network questionnaire will collect the following information: socio-economic information; tobacco, alcohol, and drug use; whether the patient knows other people diagnosed with TB within the previous year and if so, when that contact took place; place of residence; and areas to which patient travelled within the past year, places where the patient has spent time at work or socially within the past year, who the patient has spent time with over the past year and the duration of that contact.

M. tuberculosis culture will be done from sputum using Microscopic Observation Drug Susceptibility (MODS) Assay which is a rapid culture-based for primary culture in parallel with RIF- and INH-resistance. Phenotypic DST using MGIT960 to seven TB drugs (RIF, INH, STR, EMB, OFL, KAN, CAP) will be done to all isolates. Additionally, MIC of 12 TB drugs will be measured for respective isolates, with respect to: RIF, INH, OFL, MXF, AMI, STR, RFB, PAS, ETH, CYC, KAN, EMB)

DNA from positive culture will then be extracted using a commercial kit and sent for Whole Genome Sequencing on an Illumina HiSeq2000 instrument (Illumina, Inc, San Diego, CA) using 2x100 bp paired-end reads. After sequencing, the raw FASTQ sequence reads will be filtered, including removal of adapter

sequences, contamination, and low-quality reads that had more than 10% N base calls or had a quality score 4 in more than 40% of the bases. Raw FASTQ sequencing files will be uploaded for analysis.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified *M. tuberculosis* isolates from the sub-study will be stored with the same goal as the sharing of data. These samples could be used to understand phylogeny and drug resistance at local and international levels. A code-link will allow linking the biological specimens with data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

Participants will be informed about any results if, in the opinion of the principle investigator, they are considered to be relevant to them. With respect to evidence of drug resistance, the attending doctor for such patients will be expected to make a judgement call about the relevance of the finding to the patient's care at the time the result is received, and to act accordingly.

Patient confidentiality is extended beyond their basic clinical and demographic data to cover testing of biological samples and genetic tests. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

11.6 SAFETY

The following procedures and evaluations will be done as part of the study to monitor safety.

- Interviews: all interviews of TB patients will be conducted in private and in confidence, under an SOP, and will include Personal Protection Equipment (PPE) for interviewer and interviewee.
- Sputum sampling and culture: Sputum must be taken in a sputum collection room (if available) or outside of the building. The study nurse must coach study participant on how to cough sputum. Sputum processing and culture will be done in the TB research laboratory equipped with Biosafety Cabinet Level 2A for sputum processing and culturing.
- DNA extraction will be done in an accredited laboratory, following standard safety precautions under an SOP. In our previous study, we re-inoculated 75 DNA samples after extraction on Middelbrook 7H10 (media selective for *M. tuberculosis*) and we did not see any growth of the mycobacterium after 60 days of incubation.

11.7 ANALYSIS

The sub-study is a pilot study to inform the design of a large transmission study. Therefore, the sample size has been calculated based on practical considerations such as the minimum size the researchers

believe is required to provide input data to that design and what can be achieved with the available budget.

We will use whole genome sequencing to: assess the sensitivity and specificity of Whole genome sequencing as a predictor of drug resistance phenotypes as determined by routine drug susceptibility testing; and to will evaluate social and spatial connectivity as a function of genomic differences.

Comparison of genotypic and phenotypic resistance

Genotypic predictions of resistance will be based on mutations in, or upstream of, genes associated with resistance to isoniazid (ahpC, inhA, fabG1, katG), rifampicin (rpoB), ethambutol (embA, embB, embC), and pyrazinamide (pncA). Isolates containing resistance-mutations will be classified as genotypically resistant whereas those containing only wild-type sequence, or mutations considered consistent with susceptibility, will be considered susceptible. Using phenotypic results as a gold-standard, we will estimate sensitivity, specificity, negative and positive predictive value for the correct assignment of susceptibility or resistance. The χ^2 test will be used to statistically test the association between *M. tuberculosis* lineage and drug susceptibility. Cohen's k will be used to determine the level of agreement between WGS and phenotypic DST for first-line drugs. In addition, enrichment values will be calculated for drug resistance per lineage based on the ratio of lineage-specific observed and expected occurrence of drug resistance. The ratios will be visualised in a heat map as a measure of association between *M. tuberculosis* lineage and drug susceptibility.

Genomic and social network analyses

Genomic data can also be used to infer spatial and social distances within a transmission network. Here, we will determine pairwise distances between each of the 150 TB patients in the sub-study, after removing snps in highly repetitive genes such as the PE/PPE genes and in loci under strong selection (drug resistance mutations). Using snp distances as the gold standard for "epidemic proximity," we will determine whether snp distances are a function of spatial distance, age assortativeness, and other shared social activities (attendance at a specific school or religious institution, shared work-place). These data will help inform the future design of a transmission study based on whole genome sequencing.

For all possible pairs of samples, we will estimate measures of geographic distance using the Open Source Routing Machine, which is a publicly available tool that analyzes OpenStreetMap road network data, to obtain the shortest motor vehicle travel time between points in minutes. We will also calculate great-circle distances between points using the geosphere package in R, which takes into account the Earth's ellipsoid shape.

In previous work, we have determined that close genetic relatedness is best represented by a difference of ≤ 1 snp. We will therefore estimate odds ratios comparing the odds of having ≤ 1 snp pairwise distance for a range of spatial and social distances (age differences, socioeconomic distances, attends same school/religious institution/workplace, and travel time to the odds of close genetic relatedness for some specified reference value for each measure. For example, for spatial distance, we will compare the odds of any pair having \leq snp difference for a range of travel time distances compared to the odds of a 30 minute or more travel time distance. For these measures of association, we will obtain 95% Wald confidence intervals from jackknife standard errors. Jackknifing will be performed by sequentially excluding each study participant from the analysis.

12 ABBREVIATIONS

AE	Adverse Event
COC	Certificate of Confidentiality
CRF	Case Report Form
DCC	Data Coordinating Center
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
eCRF	Electronic Case Report Forms
GCP	Good Clinical Practice
WGS	Whole Genome Sequencing
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
MOP	Manual of Procedures
PI	Principal Investigator
CHC	Community Health Centre
PP	Private practitioner
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOP	Standard Operating Procedure
UP	Unanticipated Problem

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

[illegible]

14 REFERENCES

1. Republic of Indonesia, Ministry of Health National Institute of Health Research and Development, and Directorate General of Disease Control and Environmental Health; Indonesia prevalence survey 2014-15. Jakarta: June 2015. Report No.
2. World Health Organisation. The Republic of Indonesia Joint External Monitoring Mission: Tuberculosis. Jakarta: 2016 January 2017. Report No.
3. Mahendradhata Y, Lestari T, Probandari A, Indriarini LE, Burhan E, Mustikawati D, Utarini A. How do private general practitioners manage tuberculosis cases? A survey in eight cities in Indonesia. *BMC research notes*. 2015;8:564.
4. Irawati SR, Basri C, Arias MS, Prihatini S, Rintiswati N, Voskens J, Kimerling ME. Hospital DOTS linkage in Indonesia: a model for DOTS expansion into government and private hospitals. *Int J Tuberc Lung Dis*. 2007;11(1):33-9.
5. Surya A, Setyaningsih B, Suryani Nasution H, Gita Parwati C, Yuzwar YE, Osberg M, Hanson CL, Hymoff A, Mingkwan P, Makayova J, Gebhard A, Waworuntu W. Quality Tuberculosis Care in Indonesia: Using Patient Pathway Analysis to Optimize Public-Private Collaboration. *J Infect Dis*. 2017;216(suppl_7):S724-S32.
6. World Health Organisation. PPM DOTS in Indonesia: a strategy for action. World Health Organisation, department TsaoST; 2003 WHO/CDS/TB/2003.326.
7. Probandari A, Utarini A, Hurtig AK. Achieving quality in the Directly Observed Treatment Short-course (DOTS) strategy implementation process: a challenge for hospital Public-Private Mix in Indonesia. *Global health action*. 2008;1.
8. Reviono R, Setianingsih W, Damayanti KE, Ekasari R. The dynamic of tuberculosis case finding in the era of the public-private mix strategy for tuberculosis control in Central Java, Indonesia. *Global health action*. 2017;10(1):1353777.
9. Lestari BW, Arisanti N, Siregar AYM, Sihalohe ED, Budiman G, Hill PC, Alisjahbana B, McAllister S. Feasibility study of strengthening the public-private partnership for tuberculosis case detection in Bandung City, Indonesia. *BMC research notes*. 2017;10(1):404.
10. Lei X, Liu Q, Escobar E, Philogene J, Zhu H, Wang Y, Tang S. Public-private mix for tuberculosis care and control: a systematic review. *Int J Infect Dis*. 2015;34:20-32.
11. Artawan Eka Putra IW, Utami NW, Suarjana IK, Duana IM, Astiti CI, Putra IW, Probandari A, Tiemersma EW, Wahyuni CU. Factors associated to referral of tuberculosis suspects by private practitioners to community health centres in Bali Province, Indonesia. *BMC health services research*. 2013;13:445.
12. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-81.
13. Trauner A, Borrell S, Reither K, Gagneux S. Evolution of Drug Resistance in Tuberculosis: Recent Progress and Implications for Diagnosis and Therapy. *Drugs*. 2014.
14. Koser CU, Bryant JM, Becq J, Torok ME, Ellington MJ, Marti-Renom MA, Carmichael AJ, Parkhill J, Smith GP, Peacock SJ. Whole-genome sequencing for rapid susceptibility testing of *M. tuberculosis*. *The New England journal of medicine*. 2013;369(3):290-2.
15. Koser CU, Ellington MJ, Cartwright EJ, Gillespie SH, Brown NM, Farrington M, Holden MT, Dougan G, Bentley SD, Parkhill J, Peacock SJ. Routine use of microbial whole genome sequencing in diagnostic and public health microbiology. *PLoS pathogens*. 2012;8(8):e1002824.
16. Gardy JL, Johnston JC, Ho Sui SJ, Cook VJ, Shah L, Brodtkin E, Rempel S, Moore R, Zhao Y, Holt R, Varhol R, Birol I, Lem M, Sharma MK, Elwood K, Jones SJ, Brinkman FS, Brunham RC, Tang P. Whole-genome sequencing and social-network analysis of a tuberculosis outbreak. *N Engl J Med*. 2011;364(8):730-9.
17. Marais BJ, Mlambo CK, Rastogi N, Zozio T, Duse AG, Victor TC, Marais E, Warren RM. Epidemic spread of multidrug-resistant tuberculosis in Johannesburg, South Africa. *J Clin Microbiol*. 2013;51(6):1818-25.
18. Glynn JR, Vynnycky E, Fine PE. Influence of sampling on estimates of clustering and recent transmission of *Mycobacterium tuberculosis* derived from DNA fingerprinting techniques. *Am J Epidemiol*. 1999;149(4):366-71.
19. Malakmadze N, Gonzalez IM, Oemig T, Isadienso I, Rembert D, McCauley MM, Wand P, Diem L, Cowan L, Palumbo GJ, Fraser M, Ijaz K. Unsuspected recent transmission of tuberculosis among high-risk groups: implications of universal tuberculosis genotyping in its detection. *Clin Infect Dis*. 2005;40(3):366-73.

20. Schurch AC, Kremer K, Daviana O, Kiers A, Boeree MJ, Siezen RJ, van Soolingen D. High-resolution typing by integration of genome sequencing data in a large tuberculosis cluster. J Clin Microbiol. 2010;48(9):3403-6.